CHILDREN'S ONCOLOGY GROUP

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Guideline for Antibacterial Prophylaxis Administration in Pediatric Cancer and Hematopoietic Stem Cell Transplantation

COG Supportive Care Endorsed Guidelines

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The "Guideline for Antibacterial Prophylaxis Administration in Pediatric Cancer and Hematopoietic Stem Cell Transplantation" developed by the Pediatric Oncology Group of Ontario was endorsed by the COG Supportive Care Guideline Committee in June 2020.

The source clinical practice guideline is published (Lehrnbecher T, Fisher BT, Phillips B, et al. Guideline for antibacterial prophylaxis administration in pediatric cancer and hematopoietic stem cell transplantation. *Clinical Infectious Diseases* 2020; 71 (1): 226-36.) and is available at: https://doi.org/10.1093/cid/ciz1082.

The purpose of the source clinical practice guideline is to provide recommendations for systemic antibacterial prophylaxis administration in pediatric patients with cancer and recipients of hematopoietic stem cell transplant. These recommendations are presented in the table below.

Summary of Recommendations for Antibacterial Prophylaxis Administration in Pediatric Cancer and Hematopoietic Stem Cell Transplantation

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
Which pediatric patients with cancer and HSCT recipients (if any) should routinely receive systemic antibacterial prophylaxis?	
1. Consider systemic antibacterial prophylaxis administration in children with AML and relapsed ALL receiving intensive chemotherapy expected to result in severe neutropenia (absolute neutrophil count <500/µL) for at least 7 days. *Remarks*: This is a weak recommendation because the benefits of prophylaxis were closely balanced against its known and potential impacts on resistance. The panel valued what is known about efficacy and resistance outcomes of prophylaxis administered within the finite time frame of a clinical trial among enrolled participants but also considered the less certain impacts of a universal prophylaxis strategy at both the patient and institutional level. Limiting prophylaxis to patient populations at highest risk of fever and neutropenia, bacteremia, and infection-related mortality could limit antibiotic utilization to those most likely to benefit from prophylaxis. Careful discussion with patients and families about the potential risks and benefits of prophylaxis is important. Understanding local resistance epidemiology is critical to the decision of whether to implement prophylaxis.	Weak recommendation High-quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
2. We suggest that systemic antibacterial prophylaxis not be used routinely for children receiving induction chemotherapy for newly diagnosed ALL. *Remarks:* The panel acknowledged the paucity of direct contemporary randomized data applicable to children living in high-income countries. A recommendation to provide universal systemic prophylaxis to this group could have a substantial impact on institutions, given that ALL is the most common cancer diagnosis in children. There is great variability in duration of neutropenia and risk of bacteremia based on treatment protocol and patient-level characteristics. Further data are required to identify subgroups of pediatric patients with ALL who might particularly benefit from prophylaxis.	Weak recommendation Low-quality evidence
3. Do not use systemic antibacterial prophylaxis for children whose therapy is not expected to result in severe neutropenia (absolute neutrophil count severe neutropenia (absolute neutrophil count <500/µL) for at least 7 days. *Remarks*: This strong recommendation was based on reduced chance of benefit combined with continued risk of harm associated with systemic antibacterial prophylaxis.	Strong recommendation Moderate-quality evidence
4. We suggest that systemic antibacterial prophylaxis not be used routinely for children undergoing autologous HSCT. *Remarks:* This weak recommendation against routine use of antibacterial prophylaxis in autologous HSCT recipients acknowledged the risk reduction of bacteremia among this cohort. However, the panel believed that the lower baseline risk of bacteremia resulted in the impact on resistance (known and potential) outweighing the benefits. The moderate quality of evidence reflected the lack of granular data specifically in autologous HSCT recipients rather than HSCT patients as a group.	Weak recommendation Moderate-quality evidence
5. We suggest that systemic antibacterial prophylaxis not be used routinely for children undergoing allogeneic HSCT. *Remarks*: The panel acknowledged that the granularity of available data did not allow a different recommendation for allogeneic compared with autologous HSCT recipients. However, the panel noted that allogeneic HSCT recipients often have preceding conditions that could be associated with prophylaxis (eg, AML or relapsed ALL) and have prolonged neutropenia during the HSCT process, which could influence the effectiveness and adverse effects associated with prophylaxis.	Weak recommendation Moderate-quality evidence

RECOMMENDATIONS	Strength of Recommendation and Quality of Evidence*
Which agents should be used for systemic antibacterial prophylaxis in children with cancer and HSCT recipients?	
6.Levofloxacin is the preferred agent if systemic antibacterial prophylaxis is planned. *Remarks:* The strong recommendation to use levofloxacin is related to direct contemporary data in children and its microbiological spectrum of activity. If levofloxacin is not available or not able to be used, ciprofloxacin is an alternative, although lack of activity against gram-positive bacteria including viridans group streptococci may reduce the benefits of prophylaxis. Patients and families should be informed about potential short- and long-term fluoroquinolone-related adverse effects. Understanding local resistance epidemiology is critical to the decision of whether to implement fluoroquinolone prophylaxis. If fluoroquinolones are not available or cannot be used, providing no systemic antibacterial prophylaxis is an important option to consider.	Strong recommendation Moderate-quality evidence
When should systemic antibacterial prophylaxis be started and stopped?	
7.If systemic antibacterial prophylaxis is planned, we suggest that administration be restricted to the expected period of severe neutropenia (absolute neutrophil count <500/µL). *Remarks*: This is a weak recommendation based on low-quality evidence because there are no trials that compared different start and stop criteria. In general, trials administered prophylaxis during severe neutropenia and thus this recommendation reflects the available evidence and the panel's desire to minimize duration of prophylaxis administration.	Weak recommendation Low-quality evidence

*see Appendix 1

Appendix 1: GRADE

Strength of Recommendations:

Strong Recommendation	When using GRADE, panels make strong recommendations when they are confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.
Weak or Conditional Recommendation	Weak or conditional recommendations indicate that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is less confident.

Strength of Recommendation Determinants:

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Certainty in evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted

Certainty in Evidence or Quality of Evidence

High Certainty/Quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate Certainty/Quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low Certainty/Quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very Low Certainty/Quality	Any estimate of effect is very uncertain

Guyatt, G.H., et al., *GRADE: an emerging consensus on rating quality of evidence and strength of recommendations.* BMJ, 2008; 336: 924-926.
Guyatt, G.H., et al., *GRADE: going from evidence to recommendations.* BMJ, 2008; 336: 1049-1051.